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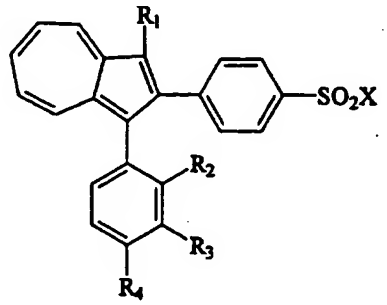
(54) 2-Phenylazulene derivatives and a process for their synthesis

(57) 2-Phenylazulenes of the formula (I) are described:



(I)

wherein
R_1 is hydrogen, lower alkoxycarbonyl, carboxy, carboxymethyl, a halogen, lower alkyl, phenyl or lower alkanoyl;
R_2, R_3 and R_4, which are the same or different, are hydrogen, lower alkyl, lower alkoxy or a halogen; and
X is lower alkyl or amino; and the pharmaceutically acceptable salts thereof. These compounds are inhibitors of cyclooxygenase-2 and are therefore useful in treating inflammation, pain and fever. Processes for the production of the compounds and a pharmaceutical composition containing them are also described.

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2-Phenylazulene derivatives and a manufacturing method of these compounds

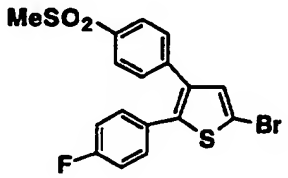
This invention relates to the novel azulene derivatives which have a cyclooxygenase-2 inhibitory action, the pharmaceutically acceptable salt thereof and the production methods thereof, further relates to a medicine composition containing said the azulene derivatives or the salt thereof.

Inflammation is the process of disorders which are characterized by flushing, fever, swelling and pain. Arthritis is the frequently generated inflammation disorder and is the most severely disorder. Wound and infectious disease are also involved the inflammation.

Non-steroidal antiinflammatory drugs (NSAIDs) represented by aspirin and indomethacin have been widely used for treatment by inflammation. The therapeutic effect of NSAIDs is related to their capacity to inhibition of the formation of prostaglandins (PGs) via the cyclooxygenase (COX) pathway. However, the most common NSAIDs can produce side effect such as gastrointestinal irritation and suppression of renal function by the inhibition of COX enzyme, that may limit therapeutic potential.

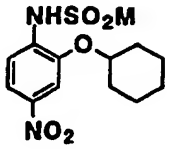
Recently, two distinct forms of COX enzyme were distinguished, a constitutive COX-1 enzyme and an inducible from of the enzyme, now commonly known as COX-2. The COX-1 enzyme is expressed in normal tissues, while COX-2 enzyme is found to be located primary in inflamed tissues. Accordingly, it seems reasonable that a selective COX-2 inhibitor could block PG production at the site of inflammation without NSAIDs - associated side effects (Meneki to Ensho, 3 (1995). Nature, 367, 215 (1994). Drug News and Perspectives, 8, 501, 1994).

Due to the novelty of this approach, the literature contains examples of selective or specific COX-2 inhibitors. Gans et al. have reported that the thiophene derivative of formula (XXVI) (J. Pat. No. 58-159489).



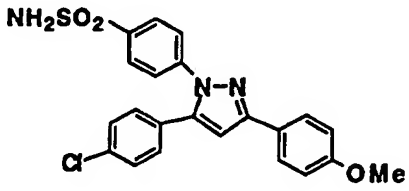
(XXVI)

Similarly, Futaki et al. have reported that the methanesulfonamide derivative of formula (XXVII) (J. Pat. No. 2-300122).

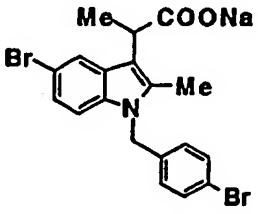


(XXVII)

Furthermore, two groups have reported that the compounds of formula (XXVIII) and (XXIX) are selective COX-2 inhibitors (WO. Pat. No. 9515318 and U. S. Pat. No. 5510368.).



(XXVIII)

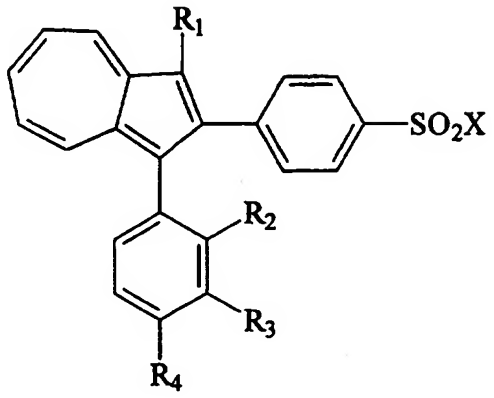


(XXIX)

The principal object of the present invention is the provision of novel compounds having antiinflammatory activity via the inhibition of the COX-2. Another object of the present invention is the provision of pharmaceutical compositions useful as antiinflammatory agents. Still other object of the present invention is the provision of new azulene derivatives and a method of the manufacture thereof. These and other objects of the invention will became apparent from the description that follows hereinafter.

This invention related to a series of new azulene derivatives which are antiinflammatory agents. Compounds of formula (I) are selective COX-2 inhibitors and are useful as antiinflammatory agents with the additional benefit of having significantly less harmful side effects. Compounds of formula (I) would be useful for the treatment of inflammation in a subject, and for treatment of other inflammation-associated disorders as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever.

The present invention provides a compound which is a 2-phenylazulene of formula (I):



(I)

wherein

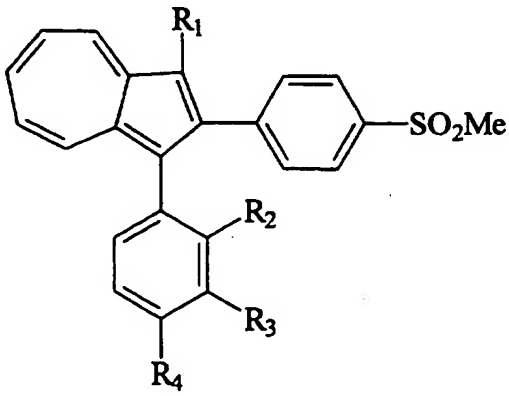
R_1 is hydrogen, lower alkoxycarbonyl, carboxy, carboxymethyl, a halogen, lower alkyl, phenyl or lower alkanoyl;

R_2, R_3 and R_4, which are the same or different, are hydrogen, lower alkyl, lower alkoxy or a halogen; and

X is lower alkyl or amino; or a pharmaceutically acceptable salt thereof.

When used to describe a functional group, the term "lower" herein means straight or branched C_1-C_5.

Thus, for instance, lower alkyl is C_1-C_5 alkyl, preferably C_1-C_4 alkyl such as methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl. Lower alkoxy is C_1-C_5 alkoxy, preferably C_1-C_4 alkoxy such as methoxy, ethoxy, i-propoxy, n-propoxy, t-butoxy, s-butoxy or n-butoxy. In one aspect of the invention the 2-phenylazulene is of formula (II)



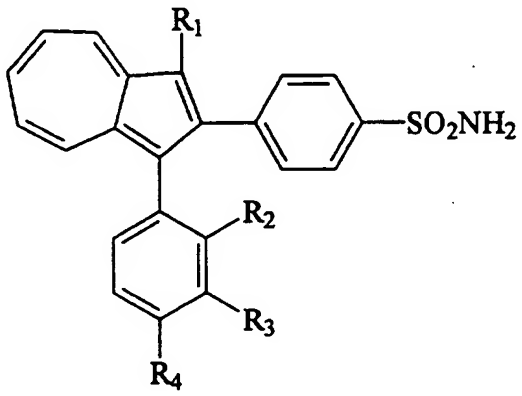
(II)

wherein

R_1 is hydrogen, methoxycarbonyl, carboxy, fluorine, chlorine, bromine, methyl, phenyl or acetyl; and

R_2, R_3 and R_4, which are the same or different, are hydrogen, methyl, methoxy, fluorine or chlorine.

In another aspect of the invention the 2-phenylazulene is of formula (III):



(III)

wherein

R_1 is hydrogen, methoxycarbonyl, carboxy, fluorine, chlorine, bromine, methyl, phenyl or acetyl; and

R_2, R_3 and R_4, which are the same or different, are hydrogen, methyl, methoxy, fluorine or chlorine.

Compounds of particular interest are those wherein, in formula (I), R_1 is hydrogen, methyl, ethyl, propyl, butyl, pentyl, phenyl, fluorine, chlorine, bromine, acetyl, propionyl, butyroyl, pentyloxy, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butoxycarbonyl, pentyloxycarbonyl or carboxy; R_2, R_3 and R_4, which are the same or different, are each hydrogen, methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propyloxy, butoxy, pentyloxy, fluorine, chlorine or bromine; and X is methyl, ethyl, propyl, butyl, pentyl or amino.

Examples of compounds of the invention are as follows:

[1] 2-(4-Methylsulfonylphenyl)-1-phenylazulene.

[2] 1-(2-Chlorophenyl)-2-(4-methylsulfonylphenyl)azulene.

[3] 1-(3-Chlorophenyl)-2-(4-methylsulfonylphenyl)azulene.

[4] 1-(4-Chlorophenyl)-2-(4-methylsulfonylphenyl)azulene.

[5] 1-(3-Fluorophenyl)-2-(4-methylsulfonylphenyl)azulene.

[6] 1-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)azulene.

[7] 1-(3-Methylphenyl)-2-(4-methylsulfonylphenyl)azulene.

[8] 1-(4-Methylphenyl)-2-(4-methylsulfonylphenyl)azulene.

[9] 1-(3-Methoxyphenyl-2-(4-methylsulfonylphenyl)azulene.

[10] 1-(4-Methoxyphenyl-2-(4-methylsulfonylphenyl)azulene.

[11] 1-(3-Chloro-4-fluorophenyl)-2-(4-methylsulfonylphenyl)azulene.

[12] 1-(3-Chloro-4-methylphenyl)-2-(4-methylsulfonylphenyl)azulene.

[13] 1-(3-Chloro-4-methoxyphenyl)-2-(4-methylsulfonylphenyl)azulene.

[14] 1-(3-Fluoro-4-methoxyphenyl)-2-(4-methylsulfonylphenyl)azulene.

[15] Methyl 2-(4-methylsulfonylphenyl)-3-phenylazulene-1-carboxylate.

[16] 2-(4-Methylsulfonylphenyl)-3-phenylazulene-1-carboxylic acid.

[17] 3-(3-Chlorophenyl)-2-(4-methylsulfonylphenyl)azulene-1-carboxylic acid.

[18] 3-(3-Chloro-4-methylphenyl)-2-(4-methylsulfonylphenyl)azulene-1-carboxylic acid.

[19] 3-(3-Chloro-4-methoxyphenyl)-2-(4-methylsulfonylphenyl)azulene-1-carboxylic acid.

[20] 3-(3-Fluoro-4-methoxyphenyl)-2-(4-methylsulfonylphenyl)azulene-1-carboxylic acid.

[21] 1-Fluoro-2-(4-methylsulfonylphenyl)-3-phenylazulene.

[22] 1-Chloro-2-(4-methylsulfonylphenyl)-3-phenylazulene.

[23] 1-Bromo-2-(4-methylsulfonylphenyl)-3-phenylazulene.

[24] 1-Methyl-2-(4-methylsulfonylphenyl)-3-phenylazulene.

[25] 1,3-Diphenyl-2-(4-methylsulfonylphenyl)azulene.

[26] 1-Acetyl-2-(4-methylsulfonylphenyl)-3-phenylazulene.

[27] 4-(1-Phenylazulene-2-yl)phenylsulfonamide.

[28] 4-[1-(3-Chlorophenyl)azulene-2-yl]phenylsulfonamide.

[29] 4-[1-(3-Fluorophenyl)azulene-2-yl]phenylsulfonamide.

[30] 4-[1-(3-Methylphenyl)azulene-2-yl]phenylsulfonamide.

[31] 4-[1-(3-Methoxyphenyl)azulene-2-yl]phenylsulfonamide.

[32] 4-[1-(3-Chloro-4-fluorophenyl)azulene-2-yl]phenylsulfonamide.

[33] 4-[1-(3-Chloro-4-methylphenyl)azulene-2-yl]phenylsulfonamide.

[34] 4-[1-(3-Chloro-4-methoxyphenyl)azulene-2-yl]phenylsulfonamide.

[35] 4-[1-(3-Fluoro-4-methoxyphenyl)azulene-2-yl]phenylsulfonamide.

[36] 2-(4-Aminosulfonylphenyl)-3-(3-chloro-4-methoxyphenylazulene-1-carboxylic acid.

[37] [2-(4-Methylsulfonylphenyl)-3-phenylazulene-1-yl]acetic acid.

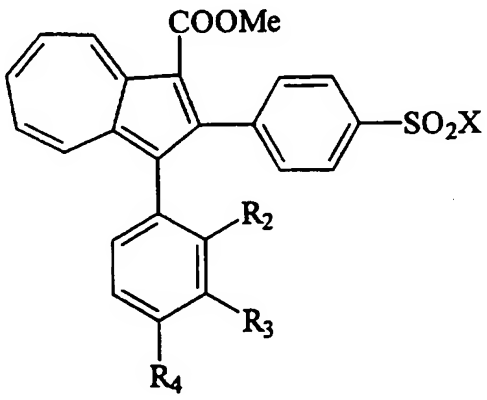
[38] 1-(3,4-Dimethoxyphenyl)-2-(4-methylsulfonylphenyl)azulene.

[39] 4-[1-(3,4-Dimethoxyphenyl)azulene-2-yl]phenylsulfonamide.

The above-mentioned compounds numbered from 1 to 39 will be referred to herein after, as compound 1, compound 2, ... compound 39, respectively.

The present invention further provides processes for producing compounds of the invention.

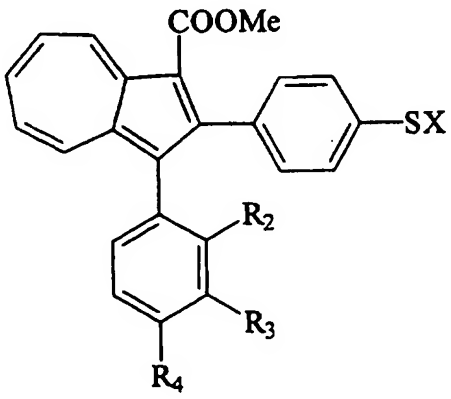
Accordingly, there is provided a process for producing a compound of the invention as defined above wherein, in formula (I), R_1 is hydrogen and X is lower alkyl, which process comprises treating, with an acid, a compound of formula (X):



(X)

wherein X is lower alkyl and R_2, R_3 and R_4 are as defined above.

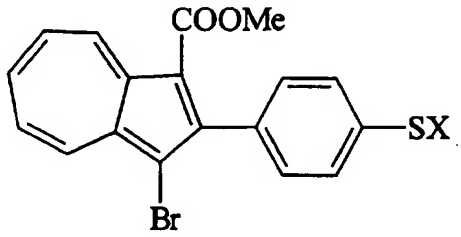
In a first aspect this process comprises the further step of producing the compound of formula (X) by oxidising a compound of formula (IX):



(IX)

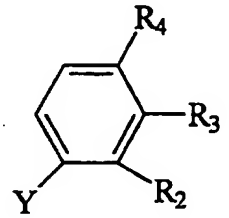
wherein X is lower alkyl and R_2, R_3 and R_4 are as defined above.

The compound of formula (IX) may be produced by the further step of producing the compound of formula (IX) by reacting a compound of formula (VII):



(VII)

wherein X is lower alkyl, with a compound of formula (VIII):

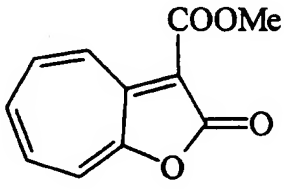


(VIII)

wherein Y is $B(OH)_2$ or $SnMe_3$ and R_2, R_3 and R_4 are as defined above.

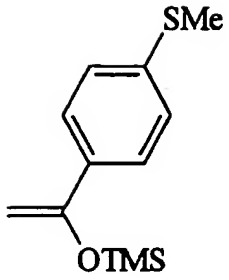
The compound of formula (VII) may be produced by the further step of

(i) reacting a compound of formula (IV):



(IV)

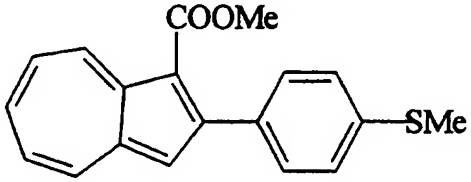
with a compound of formula (V):



(V)

wherein OTMS is a trimethylsilyloxy group; and

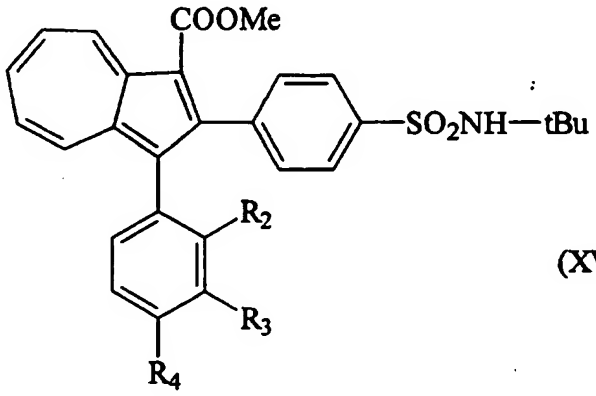
(ii) brominating the resulting compound of formula (VI):



(VI)

wherein X is as defined above, to yield the desired compound of formula (VII).

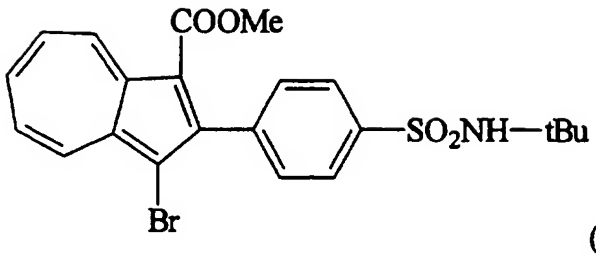
In a second aspect the present invention provides a process for producing a compound of the invention as defined above wherein, in formula (I), R_1 is hydrogen and X is amino, which process comprises treating, with an acid, a compound of formula (XVI):



(XVI)

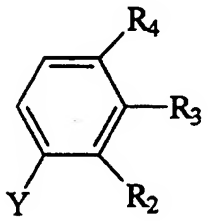
wherein R_2, R_3 and R_4 are as defined above.

The compound of formula (XVI) may be produced by the further step of reacting a compound of formula (XV):



(XV)

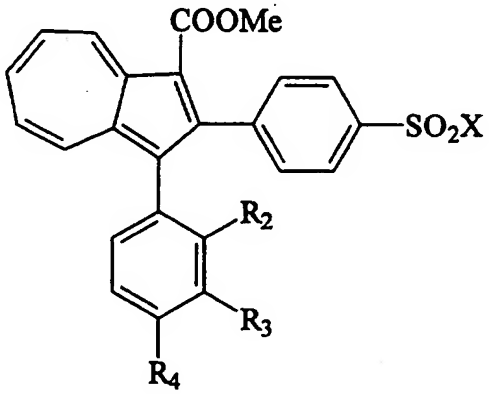
with a compound of formula (VIII):



(VIII)

wherein Y is $B(OH)_2$ or $SnMe_3$ and R_2, R_3 and R_4 are as defined above.

In a third aspect, the present invention provides a process for producing a compound of the invention as defined above wherein, in formula (I), R_1 is carboxy, which process comprises hydrolysing a compound of formula (XVIII):



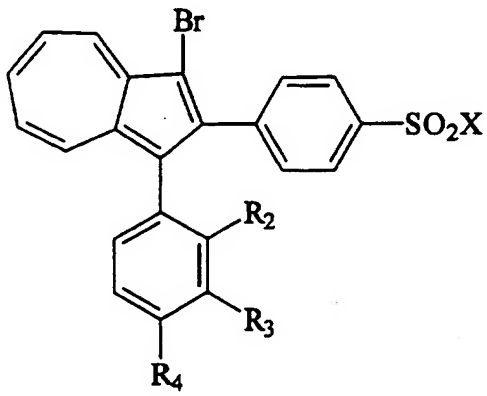
(XVIII)

wherein X, R_2, R_3 and R_4 are as defined above.

In a fourth aspect the present invention provides a process for producing a compound of

the invention as defined above wherein, in formula (I), R_1 is fluorine, chlorine or bromine, which process comprises halogenating a corresponding compound of the invention as defined above wherein, in formula (I), R_1 is hydrogen.

In a fifth aspect the present invention provides a process for producing a compound of the invention as defined above wherein, in formula (I), R_1 is lower alkyl or phenyl, which process comprises reacting a compound of formula (XXI):



(XXI)

wherein X, R_2, R_3 and R_4 are as defined above, with a compound of formula (XXII):

$$R_6-B(OH)_2 \qquad \text{(XXII)}$$

wherein R_6 is lower alkyl or phenyl.

In a sixth aspect the present invention provides a process for producing a compound of the invention as defined above wherein, in formula (I), R_1 is lower alkanoyl, which process comprises acylating, by a Friedel-Crafts reaction, a corresponding compound of the invention as defined above wherein, in formula (I), R_1 is hydrogen.

In a seventh aspect the present invention provides a process for producing a compound of the invention as defined above wherein, in formula (I), R_1 is carboxymethyl, which process comprises:

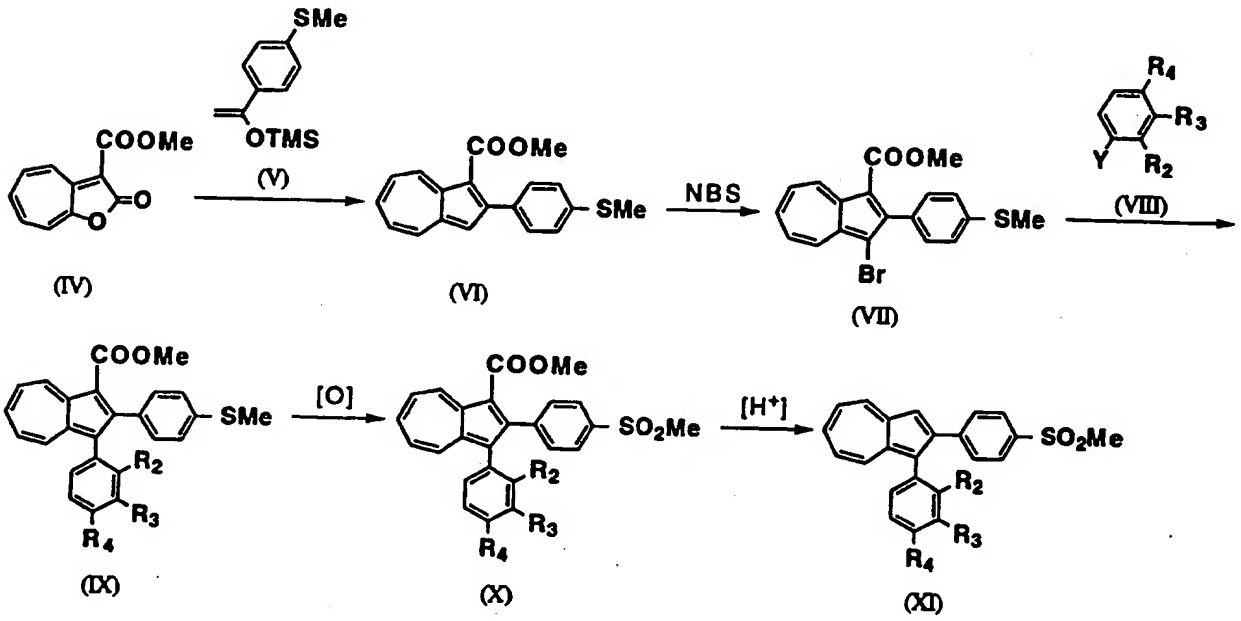
(i) treating a corresponding compound as defined above wherein, in formula (I), R_1 is lower alkanoyl, with sulphur in the presence of a secondary amine by the Wilgerodt-kindler reaction; and

(ii) hydrolysing the resulting thioamide derivative under acidic or basic conditions to yield the desired compound.

In any of the above aspects the process of the present invention may comprise the further step of converting the resulting 2-phenylazulene of formula (I) into a pharmaceutically acceptable salt thereof.

The processes for producing compounds of the invention are illustrated in the following schemes 1-6.

Scheme 1



In the scheme each of R_2, R_3 and R_4 is as defined above, Y is $B(OH)_2$ or $SnMe_3$ and TMS represents trimethylsilyl.

Scheme 1 shows the preparation of 2-(4-methylsulfonylphenyl)azulene derivatives. Compound (IV), which is a starting material (IV) in this sequence, is synthesized according to a reported method (Tetrahedron, 27, 6023, 1971). In step 1, compound (IV) is converted into compound (VI) by reaction with silyl enol ether (V). The silyl enol ether (V) is prepared according to the reported method (Journal of medicinal chemistry, 39, 253, 1996). The preferred reaction temperature for this step is in the range from about 160°C up to the reflux temperature of the reaction mixture.

In step 2, the bromination of compound (VI) using *N*-bromsuccinimide (NBS) or

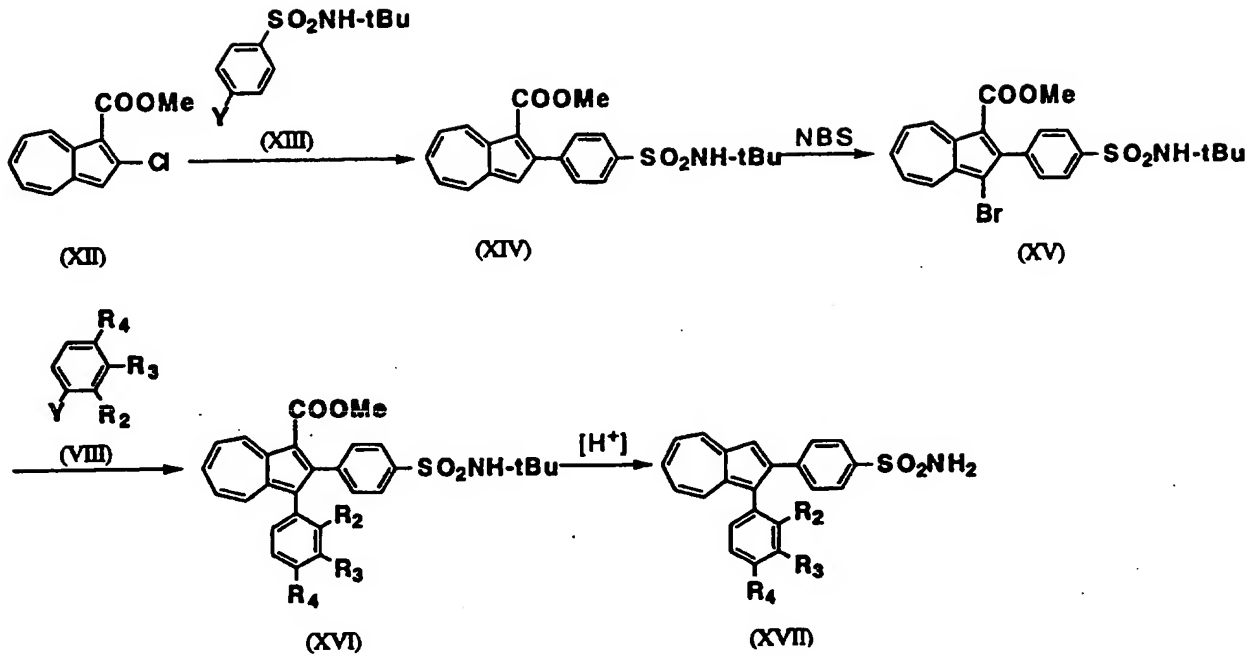
bromine gives the compound (VII). This reaction is carried out in the presence of radical initiators such as α,α'-azobis(isobutyronitrile) and benzoylperoxide in carbon tetrachloride as reaction solvent at the reflux temperature of the reaction mixture.

In step 3, compound (VII) is coupled with compound (VIII) to give compound (IX). In the case of Y being $B(OH)_2$ in the formula (VIII), the reaction is carried out using palladium catalyst in the presence of a base according to a reported method (Synthetic communications, 11, 513, 1981). Tetrakis(triphenylphosphine)palladium (0), bis(triphenylphosphine)palladium chloride (2) and palladium chloride (2) can be used as catalysts. This reaction is carried out in the presence of a base such as sodium hydrogencarbonate, sodium carbonate, sodium methoxide, triethylamine or pyridine. Preferred reaction solvents for use in this coupling reaction include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N,N*-dimethylformamide and water. In general, this reaction is carried out in the range from 80°C up to 120°C.

Alternatively, compound (IX) can be obtained using a tin reagent instead of boronic acid. In the case where Y is $SnMe_3$ in formula (VIII), the reaction is carried out using a palladium catalyst according to a reported method (Angewande Chemie, international edition in English, 25, 508, 1986). Tetrakis(triphenylphosphine)palladium (0), bis(tripenylphosphine)palladium chloride (2) and palladium chloride (2) can be used as catalysts. Preferred reaction solvents for use in this coupling include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N,N*-dimethylformamide and water. In general, this reaction is carried out in the range from 80°C up to 120°C.

In step 4, compound (IX) is oxidized to compound (X) in reaction solvents such as methanol, ethanol, dichloromethane, tetrahydrofuran and water. Hydrogen peroxide, *m*-chloroperbenzoic acid, oxone and sodium periodate are suitable for oxidation and the reaction is carried out at a temperature ranging from room temperature up to the reflux temperature of the reaction mixture. In step 5, compound (X) is treated with acids such as sulfuric acid, *p*-toluenesulfonic acid, trifluoroacetic acid, phosphoric acid and malic acid to give compound (XI). Preferred reaction solvents include benzene and toluene, and the reaction is carried out in the range of from 70°C to 110°C.

Scheme 2



In scheme 2 each of R_2, R_3, R_4 and Y are as defined above.

Scheme 2 shows the preparation of sulfonamide derivatives. Compound (XIII) is synthesized according to a reported method (Journal of organic chemistry, 40, 1689, 1975). In step 1, compound (XII) is coupled with compound (XIII) to give the compound (XIV). In the case of Y being $B(OH)_2$ in the formula (XIII), the reaction is carried out using palladium catalyst in the presence of base according to a reported method (Synthetic communications, 11, 513, 1981). Tetrakis (triphenylphosphine)palladium (0), bis(triphenylphosphine) palladium chloride (2) and palladium chloride (2) can be used as a catalyst. This reaction is carried out in the presence of base such as sodium hydrogencarbonate, sodium carbonate, sodium methoxide, triethylamine and pyridine. Preferred reaction solvents for use in the coupling include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N,N*-dimethylformamide and water. In general, this reaction is carried out at the reflux temperature of the reaction mixture.

Alternatively, compound (XIV) can be obtained using a tin reagent instead of boronic acid. In the case of Y being $SnMe_3$ in formula (XIII), the reaction is carried out using a palladium catalyst according to a reported method (Angewande Chemie, international edition in English, 25, 508, 1986). Tetrakis (triphenylphosphine)palladium (0),

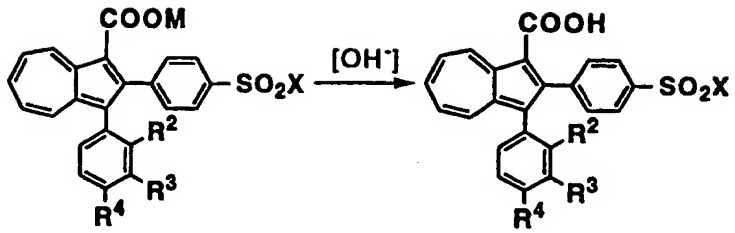
bis(triphenylphosphine)palladium chloride (2) and palladium choride (2) can be used as catalysts. Preferred reaction solvents for use in this coupling include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N*-*N*-dimethylformamide and water. In general, this reaction is carried out at the reflux temperature of the reaction mixture. In step 2, the bromination of compound (XIV) using *N*-bromosuccinimide or bromine gives the compound (XV). This reaction is carried out in the presence of radical initiators such as α,α'-azobis(isobutyronitrile) and benzoylperoxide in carbon tetrachloride as reaction solvent at the reflux temperature of the reaction mixture.

In step 3, compound (XV) is coupled with compound (VIII) to give compound (XVI). In the case of Y being $B(OH)_2$ in the formula (VIII), the reaction is carried out using a palladium catalyst in the presence of a base according to a reported method (Synthetic Communications, 11, 513, 1981). Tetrakis (triphenylphosphine)palladium (0), bis (triphenylphosphine) palladium chloride (2) and palladium chloride (2) can be used as catalysts. This reaction is carried out in the presence of a base such as sodium hydrogencarbonate, sodium carbonate, sodium methoxide, triethylamine and pyridine. Preferred reaction solvents for use in this coupling include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N,N*-dimethylformamide and water. In general, this reaction is carried out at the reflux temperature of the reaction mixture.

Alternatively, compound (XVI) can be obtained using a tin reagent instead of boronic acid. In the case of Y being $SnMe_3$ in formula (VIII), the reaction is carried out using a palladium catalyst according to a reported method (Angewandte Chemie, international edition in English, 25, 508, 1986). Tetrakis (triphenylphosphine)palladium (0), bis(triphenylphosphine)palladium chloride (2) and palladium chloride (2) can be used as catalysts. Preferred reaction solvents for use in this coupling reaction include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N,N*-dimethylformamide and water. In general, this reaction is carried out at the reflux temperature of the reaction mixture.

In step 4, demethoxycarbonylation of compound (XVI) under acidic conditions proceeds simultaneously with deprotection of the *t*-butyl group to give the compound (XVII). Sulfuric acid, *p*-toluene sulfonic acid, trifluoroacetic acid and phosphoric acid are suitable acids and the reaction is carried out in reaction solvents such as benzene or toluene at the reflux temperature of the reaction mixture.

Scheme 3

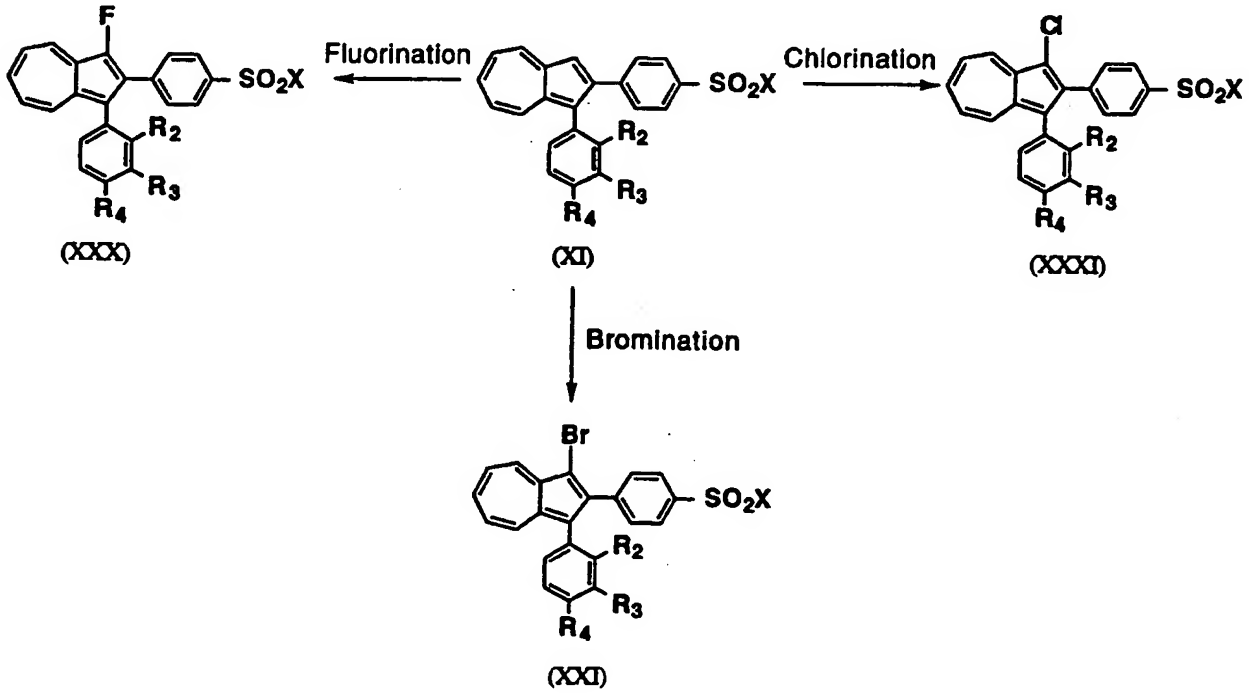


(X) (XIX)

In this scheme each of R_2, R_3, R_4 and X are as defined above.

Scheme 3 shows the preparation of carboxylic acid derivatives. Compounds (X), which is synthesized in scheme 1, is hydrolyzed under basic conditions to give the compound (XIX). The aqueous solutions of sodium hydroxide, potassium hydroxide or lithium hydroxide can be employed for the hydrolysis and this reaction is carried out in reaction solvents such as methanol, ethanol, tetrahydrofuran or dioxane under the reflux temperature of the reaction mixture.

Scheme 4



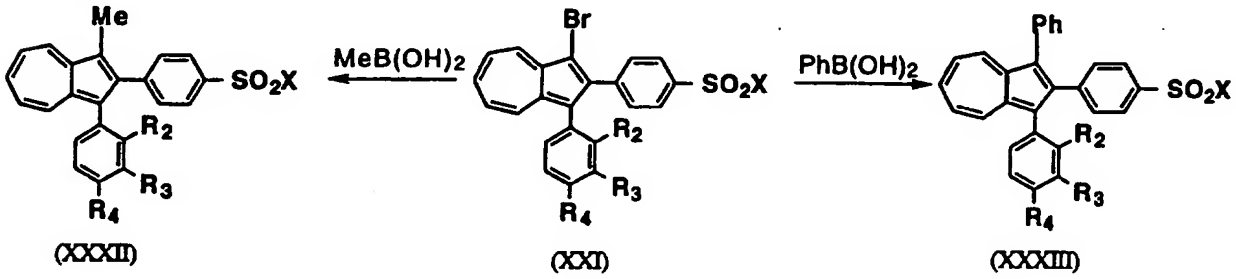
(XXX) (XI) (XXXI)

(XXI)

In this scheme each of R_2, R_3, R_4 and X is as defined above.

Scheme 4 shows the preparation of 1-halogenated azulene derivatives. Fluorination of compound (XI), which is synthesized in scheme 1, gives the compound (XXX). 1-Fluoropyridinium triflate is suitable for a fluorinating agent and this reaction is carried out in 1, 2-dichloroethane as reaction solvent at the reflux temperature of the reaction mixture. Compounds (XXXI) and (XXI) are prepared by halogenation of compound (XI) with N-chlorosuccinimide, N-bromosuccineimide or bromine. This reaction is carried out in the presence of a radical initiator such as α,α-azobis (isobutyronitrile) and benzoylperoxide in carbon tetrachloride as reaction solvent at the reflux temperature of the reaction mixture.

Scheme 5

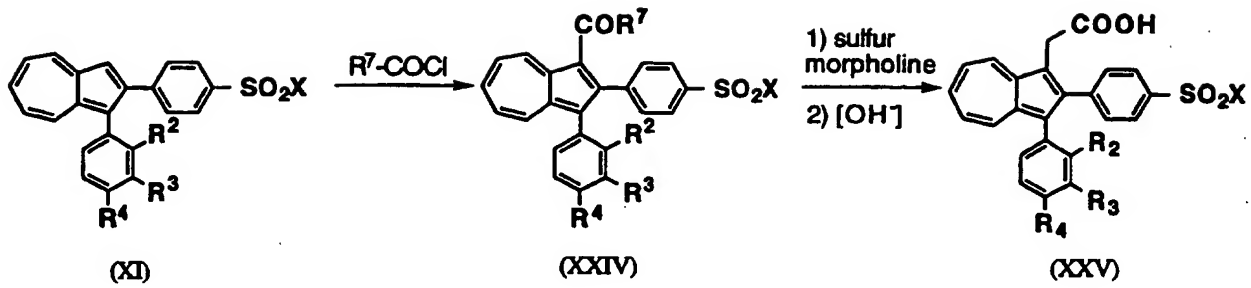


(XXXII) (XXI) (XXXIII)

In the scheme R_2, R_3, R_4 and X are as defined above.

Scheme 5 shows the preparation of 1-alkyl and 1-phenylazulene derivatives. The reaction of compound (XXI) with methylboronic acid or phenylboronic acid gives compounds (XXXII) or (XXXIII). The reaction is carried out using a palladium catalyst in the presence of a base according to reported methods (Synthetic Communications, 11, 513,1981). Tetrakis (triphenylphosphine)palladium (0), bis(triphenylphosphine)palladium chloride (2) and palladium chloride (2) can be used as catalysts. This reaction is carried out in the presence of a base such as sodium hydrogencarbonate, sodium methoxide, triethylamine or pyridine. Preferred reaction solvents for use in this coupling reaction include benzene, toluene, dioxane, tetrahydrofuran, chloroform, methanol, *N,N*-dimethylformamide and water. In general, this reaction is carried out at the reflux temperature of the reaction mixture.

Scheme 6



(XI) (XXIV) (XXV)

In this scheme each of R_2, R_3, R_4 and X are as defined above and R_7 is a methyl group.

Scheme 6 shows the preparations of 1-acylazulene and azulene-1-acetic acid derivatives. In step 1, compound (XI), which is synthesized in scheme 1, is acylated by a Friedel-Crafts reaction to give the compound (XXIV). The acid chloride can be used as acylating agent and this reaction is carried out in the presence of Lewis acids such as aluminium chloride, titanium tetrachloride, tin tetrachloride or boron trifluoride in reaction solvents such as dichloromethane, 1,1,2,2- tetrachloroethane carbondisulfide and nitrobenzene at the reflux temperature of the reaction mixture.

In step 2, the Wilgerodt-kindler reaction of compound (XXIV) gives the compound (XXV). The Wilgerodt-kindler reaction is carried out using sulfur in the presence of a secondary amine such as dimethylamine, morpholine or piperidine. The obtained thioamide derivatives are hydrolyzed under acid or basic conditions to give the compound (XXV). The aqueous solutions of hydrochloride, sulfonic acid, sodium hydroxide, potassium hydroxide and lithium hydroxide are suitable for this hydrolysis and the reaction is carried out in reaction solvents such as methanol, ethanol, tetrahydrofuran and dioxane at the reflux temperature of the reaction mixture.

The reaction products are purified as free acids or pharmaceutically acceptable alkali-addition salts using techniques such as extraction, concentration, evaporation, crystallization, filtration, recrystallization and chromatography.

The compounds of the present invention are inhibitors of cyclooxygenase-2. They may therefore be used in the treatment of inflammation and inflammation-associated disorders, pain or fever. The compounds of general formula (I) are thus useful for the treatment of

inflammation without NSAIDs-associated side effects such as gastrointestinal irritation and suppression of renal function.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents. Suitable diluents include soluble starch, lactose, sucrose, calcium carbonate and calcium phosphate. Binders include soluble starch, acacia, carboxymethylcellulose, hydroxymethylcellulose, crystalline cellulose, alginic acid, gelatin and polyvinylpyridone. Lubricants include stearic acid, magnesium stearate, calcium stearate and talc. Disintegrants include carboxymethylcellulose and talc. Pharmaceutical solvents include saline. They may be combined with various pharmaceutically acceptable inert carriers in the form of powders, granule subtilaes, tablets, capsules, external applications and injections. In one aspect of the present invention, therefore, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as an active ingredient, a compound of the invention as defined above.

The pharmaceutical composition can be administered orally. The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a daily dosage of active ingredient can be about 50 mg to 5 mg. Preferably 100 mg to 500 mg per day given in divided doses 1 to 3 times a day. The example of dosage are 10 mg, 50 mg, 100 mg, 200 mg, 500 mg and 1 g.

The inhibitory activity of compounds of the present invention on COX-1 and COX-2 were assayed according to the method of Needleman (J. Biol Chem, 254, 9772, 1979). One unit of COX-1 or COX-2 enzyme, suspended with Tris-HCl buffer (pH 8.0, 500 μl) containing 1 μM hematin as co-factor, was incubated with the compound and 1 mM arachidonic acid at 37°C for 10 min. The reaction was stopped with 50 mM indomethacin (50 μl), and amounts of PGE_2 in the reaction mixture was assayed using a PGE_2 ELISA system IC_{50} (the concentrations which inhibited PGE_2 production by 50%) were calculated and shown in Table 1.

[Table 1]

Compound	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)
1	>10	0.76
2	>10	6.9
3	>10	0.0093
4	>10	0.030
5	>10	>10
6	>10	1.2
7	>10	0.048
8	>10	7.4
9	>10	4.8
10	>10	3.7
11	>10	0.083
12	>10	0.0049
13	>10	0.019
14	>10	0.0084
21	>10	7.9
27	>10	0.0086
28	7.6	2.6
29	4.7	0.77
30	4.3	0.50
31	>10	2.5
32	>10	0.012
33	4.1	0.0026
34	0.96	0.0034
35	6.7	0.022
38	>10	0.064
39	>10	0.29

The enzymatic activity of COX involves bis-oxygenation of arachidonic acid to PGG_2, which is further reduced to PGH_2 in a peroxidase reaction by the same protein. NSAIDs prevent the

production of PGs by inhibiting the enzyme COX. Recently, two distinct forms of COX enzyme were distinguished, a constitutive COX-1 enzyme and an inducible form of the enzyme, now commonly known as COX-2. The COX-1 enzyme is expressed in normal tissues and is physiologically important for gastrointestinal and renal functions, while the previously unidentified COX-2 isoform is found to be located primarily in inflamed tissues. It seems reasonable that a selective COX-2 inhibitor could block PG production at the site of inflammation without affecting beneficial PGs in normal tissues such as stomach and renal tissue. On the other hand, compounds in this invention are expected to have a usefulness for cancer therapy. Especially, it is thought that these compounds, as other inhibitors of PG biosynthesis, inhibit the metastasis of benign or partially transformed colon polyp (Acta histochemica supplement band, 29, 195, 1990). Furthermore, COX-2 inhibitors reduce the risks of colorectal carcinoma, and it is reported that COX-2 is highly expressed in apoptosis. From these findings, it is expected to use COX-2 inhibitors for cance and apoptosis therapy (Cell, 83, 345, 1995).

The present invention is further illustrated in the Examples which follow.

Example 1: 2-(4-Methylsulfonylphenyl)-1-phenylazulene (Compound 1)

Methyl 2-(4-methylsulfonylphenyl)-3-phenylazulene-1-carboxylate (0.13 g) was treated with 100 % phosphoric acid (5.0 ml). After stirring for 10 min at 120 °C, the reaction mixture was poured into ice-water, followed by extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by SiO_2 column chromatography (benzenee/Et_2O, 50:1) to give the title compound (0.10 g) as violet crystals; mp 139-140 ℃.

^1H NMR ($CDCl_3$):δ = 3.07 (3H, s), 7.15 (1H, t), 7.21 (1H, t), 7.31 (2H, d), 7.38-7.45 (3H, m), 7.57-7.62 (4H, s+m), 7.84 (2H, d), 8.28 (1H, d), 9.39 (1H, d).

Example 2-15: The listed compounds 2-14 and 38 in Table 2 were prepared according to the procedure as example 1.

Example 16: Methyl 2-(4-methylsulfonylphenyl)-3-phenylazulene-1-carboxylate (Compound 15)

(a) Methyl 2-(4-methylthiophenyl)azulene-1-carboxylate: 3-Methoxycarbonyl-2H-cyclohepta [*b*] furan-2-one (2.00 g) and 1-(4-methylthiophenyl)-1-trimethylsilyloxy)ethylene (9.30 g) was stirred at 190 °C for 18 hr. The reaction mixture was poured into 10 % aqueous HCl, followed by extracted with EtOAc . The combined EtOAc extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by SiO_2 column chromatography (EtOAc/*n*-hexane,1:10) to give the title compound (2.70 g) as violet crystals; mp

101-102 °C.

^{1}H NMR ($CDCl_3$):δ = 2.55 (3H, s), 3.81 (3H, s), 7.31-7.34 (4H, m), 7.42 (1H, t), 7.50-7.55 (2H, m), 7.52 (2H,d), 7.73 (1H, t), 8.38 (1H, d), 9.37 (1H, d).

(b) Methyl 3-bromo-2-(4-methylthiophenyl)azulene-1-carboxylate: To a solution of 2-(4-methylsulfonylphenyl)-1-phenylazulene (2.00 g) in CCl_4 (20.0 ml) was added *N*-bromosuccinimide (1.26 g) and α,α'-azobis(isobutyronitrile) (0.01 g), and the reaction mixture was heated under reflux for 1 hr. The mixture was filtered, and concentrated. The crude product was purified by SiO_2 column chromatography (benzene/Et_2O, 100:1) to give the title compound (2.40 g) as violet crystals; mp 98-100 °C.

^{1}H NMR (CDCl3):δ = 2.56 (3H, s), 3.71 (3H, s), 7.33-7.40 (4H, m), 7.57 (1H, t), 7.59 (1H, t), 7.83 (1H, t), 8.60 (1H, d), 9.46 (1H, d).

(c) Methyl 2-(4-methylthiophenyl)-3-phenylazulene-1-carboxylate: To a solution of methyl 3-bromo-2-(4-methylthiophenyl)azulene-1-carboxylate (0.50 g) in toluene (20.0 ml) was added phenylboronic acid (0.38 g), tetrakis(triphenylphosphine)palladium (0) (0.08 g) and 2M aqueous Na_2CO_3 (2.6 ml) , and the reaction mixture was heated under reflux for 2 hr. The mixture was poured into ice-water, followed by extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography (benzenee/EtOAc, 100:1) to give the title compound (0.49 g) as violet crystals; mp 115-116 °C.

^{1}H NMR ($CDCl_3$):δ = 2.48 (3H, s), 3.66 (3H, s), 7.10-7.38 (7H, m), 7.39 (2H, d), 7.58 (1H, t), 7.80 (2H, d), 8.36 (1H, d), 9.47 (1H, d).

(d) Methyl 2-(4-methylsulfonylphenyl)-3-phenylazulene-1-carboxlate: To a solution of methyl 2-(4-methylthiophenyl)-3-phenylazulene-1-carboxylate (0.60 g) in MeOH (10.0 ml) was added a solution of oxone (1.90 g) in water (10.0 ml), and the reaction mixture was stirred at room temperature for 16 hr, followed by extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography ($CHCl_3$/acetone, 100:1) to give the title compound (0.54 g) as green crystals; mp 69-70 °C.

^{1}H NMR ($CDCl_3$):δ = 3.07 (3H, s), 3.73 (3H, s), 7.11-7.36 (7H, m), 7.41 (2H, d), 7.60 (1H, t), 7.83 (2H, d), 8.41 (1H, d), 9.56 (1H, d).

Example 17: 2-(4-Methylsulfonylphenyl)-3-phenylazulene-1-carboxylic acid (Compound 16)

To a solution of methyl 2-(4-methylsulfonylphenyl)-3-phenylazulene-1-carboxylate (0.26 g) in

MeOH (10.0 ml) was added 10% aqueous NaOH (2.0 ml), and the reaction mixture was heated under reflux for 6 hr. After removal of solvent, the aqueous layer was washed with Et_2O. The solution was adjusted to pH 2.0 with 10 % aqueous HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography (EtOAc/MeOH, 30:1) to give the title compound (0.20 g) as violet crystals; mp 168-169 °C.

^{1}H NMR ($CDCl_3$):δ = 3.23 (3H, s), 7.17 (2H, d), 7.30-7.37 (3H, m), 7.45 (2H, d), 7.58 (1H, t), 7.71 (1H, t), 7.80 (2H, d), 7.98 (1H, t), 8.33 (1H, d), 9.55 (1H, d), 12.35 (1H, bs).

Example 18-22: The listed compounds 17-20 and 36 in Table 2 were prepared according to the procedure as example 17.

Example 23: 1-Fluoro-2-(4-methylsulfonylphenyl)-3-phenylazulene (Compound 21)

To a solution of 2-(4-methylsulfonylphenyl)-1-phenylazulene (0.20 g) in 1, 2-dichloroethane (20.0 ml) was added 1-fluoropyridinium triflate (0.28 g), and the reaction mixture was heated under reflux for 30 min. The mixture was poured into ice-water, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography (benzenee/EtOAc, 20:1) to give the title compound (0.10 g) as green crystals; mp 120-122 °C.

^{1}H NMR ($CDCl_3$):δ = 3.08 (3H, s),7.01 (2H, t), 7.06 (1H, t), 7.25-7.28 (2H, m), 7.37-7.43 (2H, m), 7.55 (1H, t), 7.61 (2H, d), 7.87 (2H, d), 8.22 (1H, d,d), 8.35 (1H, d).

Example 24: 1-Chloro-2-(4-methylsulfonylphenyl)-3-phenylazulene (Compound 22)

To a solution of 2-(4-methylsulfonylphenyl)-1-phenylazulene (0.20 g) in CCl_4 (10.0 ml) was added *N*-chlorosuccinimide (0.08 g) and α,α'-azobis(isobuthyronitrile) (0.01 g), and the reaction mixture was heated under reflux for 1 hr. The mixture was filtered, and concentrated. The crude product was purified by SiO_2 column chromatography (benzene/EtOAc, 20:1) to give the title compound (0.10 g) as green crystals; mp 140-142 °C.

^{1}H NMR ($CDCl_3$):δ = 3.09 (3H, s), 7.14-7.38 (7H, m), 7.58 (2H, d), 7.65 (1H, t), 7.89 (2H, d), 8.29 (1H, d), 8.52 (1H, d).

Example 25: 1-Bromo-2-(4-methylsulfonylphenyl)-3-phenylazulene (Compound 23)

To a solution of 2-(4-methylsulfonylphenyl)-1-phenylazulene (0.43 g) in CCl_4 (20.0 ml) was added *N*-bromosuccinimide (0.23 g) and α,α'-azobis(isobutyronitrile) (0.01 g), and the reaction mixture was heated under reflux for 1 hr. The mixture was cooled to room temperature and was filtered, and concentrated. The crude product was purified by SiO_2 column chromatography (benzene/EtOAc, 20:1) to give the title compound (0.52 g) as green crystals; mp 172-173 °C.

^{1}H NMR (CDCl3):δ = 3.10 (3H, s), 7.17-7.37 (7H, m), 7.56 (2H, d), 7.67 (1H, t), 7.89 (2H, d), 8.29 (1H, d), 8.53 (1H, d).

Example 26: 1- Methyl-2-(4-methylsulfonylphenyl)-3-phenylazulene (Compound 24)

To a solution of methyl 1-bromo-2-(4-methylsulfonylphenyl)-3-phenylazulene (0.20 g) in toluene (10.0 ml) was added methylboronic acid (0.13 g), tetrakis(triphenylphosphine)palladium (0) (0.05 g) and 2M aqueous Na_2CO_3 (0.9 ml), and the reaction mixture was heated under reflux for 2 hr. The reaction mixture was poured into ice-water, followed by extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography (benzenee/EtOAc, 20:1) to give the title compound (0.15 g) as violet crystals; mp 165-167 °C.

^{1}H NMR ($CDCl_3$):δ = 3.03 (3H, s), 7.12-7.39 (14H, m), 7.59 (1H, t), 7.66 (2H, d), 8.35 (2H, d).

Example 27: The listed compounds 25 in Table 2 were prepared according to the procedure as example 26.

Example 28: 1-Acetyl-2-(4-methylsulfonylmethyl)-3-phenylazulene (Compound 26)

To a solution of 2-(4-methylsulfonylphenyl)-1-phenylazulene (0.13 g) in CH_2Cl_2 (10.0 ml) was added anhydrous $AlCl_3$ (0.07 g) at 0 °C, and the reaction mixture was stirred for 30 min at same temperature. Then, acetyl chloride (0.04 ml) was added at same temperature, and the reaction mixture was heated under reflux for 8 hr. The mixture was poured into ice-water, and extracted with EtOAc. The combined EtOAc extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography (benzenee/EtOAc, 10:1) to give the title compound (0.12 g) as violet crystals; mp 138-139 °C.

^{1}H NMR ($CDCl_3$):δ = 2.10 (3H, s), 3.09 (3H, s), 7.14 (2H, dd), 7.13-7.35 (8H, m), 7.42 (1H, t), 7.47 (2H, d), 7.59 (1H, t), 7.82 (1H, t), 7.89 (2H, d), 8.39 (1H, d), 9.42 (1H, d).

Example 29: 4-(1-Phenylazulene-2-yl)phenylsulfonamide (Compound 27)

(a) Methyl 2-(4-*t* -butylaminosulfonylphenyl) azulene-1-carboxylate: To a solution of methyl 2-chloroazulene-1-carboxylate (0.50 g) in toluene (20.0 ml) was added 4-*t*-butylaminosulfonyl-phenylboronic acid (0.87 g), tetrakis(triphenylphosphine)palladium (0) (0.12 g), and 2M aqueous Na_2CO_3 (4.5 ml), and the reaction mixture was heated under reflux for 16 hr. The mixture was poured into ice-water, followed by extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography ($CHCl_3$/EtOAc, 100:1) to give the title compound (1.13 g) as violet crystals; mp 169-170 °C.

^1H NMR ($CDCl_3$):δ = 1.29 (9H, s), 3.74 (3H, s), 4.57 (1H, bs), 7.34 (1H, s), 7.49 (1H, t), 7.60 (1H, t), 7.65 (2H, d), 7.82 (1H, t), 7.95 (2H, d), 7.45 (1H, d), 9.52 (1H, d).

(b) Methyl 3-bromo-2-(4-*t*-butylaminosulfonylphenyl) azulene-1-carboxylate: To a solution of 2-(4-*t* - butylaminosulfonylphenyl) -1-phenylazulene (0.50 g) in CCl_4 (20.0 ml) was added *N* - bromosuccinimide (0.25 g) and α,α'-azobis (isobutyronitrile) (0.01 g), and the reaction mixture was heated under reflux for 1 hr. The reaction mixture was filtered, and concentrated. The crude product was purified by SiO_2 column chromatography (benzene/EtOAc, 20:1) to give the title compound (0.56 g) as violet crystals; mp 171-172 °C.

^1H NMR ($CDCl_3$):δ = 1.30 (9H, s), 3.62 (3H, s), 4.59 (1H, bs), 7.53 (2H, d), 7.63 (1H, t), 7.66 (1H, t), 7.91 (1H, t), 7.99 (2H, d), 8.64 (1H, d), 9.52 (1H, d).

(c) Methyl 2- (4-*t*-butylaminosulfonylphenyl) -3-phenylazulene-1-carboxylate: To a solution of methyl 3-bromo-2-(4-*t*-butylaminosulfonylphenyl) azulene-1-carboxlate (0.56 g) in toluene (10.0 ml) was added phenylboronic acid (0.34 g), tetrakis(triphenylphosphine)palladium (0) (0.07 g) and 2M aqueous Na_2CO_3 (2.3 ml), and the reaction mixture was heated under reflux for 2 hr. The reaction mixture was poured into ice-water, followed by extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography (benzenee/EtOAc, 20:1) to give the title compound (0.47 g) as violet crystals; mp 76-77 °C.

^1H NMR ($CDCl_3$):δ = 1.21 (9H, s), 3.66 (3H, s), 4.44 (1H, bs),7.11-7.28 (5H, m), 7.31 (2H, d), 7.42 (1H, t), 7.56 (1H, t), 7.78 (2H, d), 7.82 (1H, t), 8.42 (1H, d), 9.62 (1H,d).

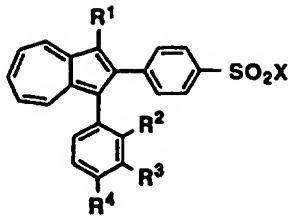
(d) 4-(1-Phenylazulene-2-yl)phenylsulfonamide (Compound 27): A mixture of methyl 2-(4-*t*-butylaminosulfonylphenyl)-3-phenylazulene-1-carboxlate (0.46 g) and 100 % phosphoric acid (12.0

ml) was heated and stirred at 110 °C for 10 min. The reaction mixture was poured into ice-water, and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by SiO_2 column chromatography ($CHCl_3$/acetone, 20:1) to give the title compound (0.25 g) as green crystals; mp 188-189 °C.

^1H NMR ($CDCl_3$):δ = 4.80 (2H, bs), 7.15 (1H, t), 7.20 (1H, t), 7.30-7.44 (5H, m), 7.54-7.62 (2H, s+t), 7.56 (2H, d), 7.82 (2H, d), 8.27 (1H, d), 8.38 (1H, d).

Example 30-38: The listed compounds 28-35 and 39 in Table 2 were prepared according to the procedure as example 29.

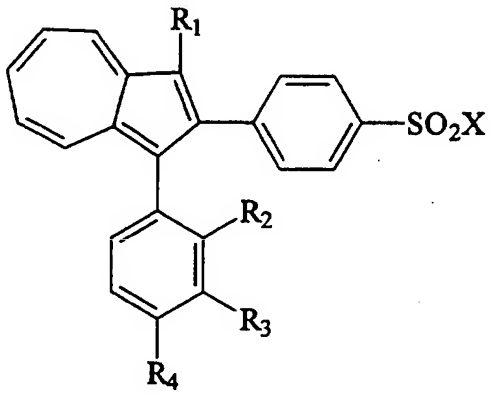
[Table 2]



Compounds	R^1	R^2	R^3	R^4	X	Melting point (℃)
1	H	H	H	H	Me	164-165
2	H	Cl	H	H	Me	175-176
3	H	H	Cl	H	Me	155-156
4	H	H	H	Cl	Me	187-188
5	H	H	F	H	Me	140-141
6	H	H	H	F	Me	151-152
7	H	H	Me	H	Me	146-147
8	H	H	H	Me	Me	178-179
9	H	H	OMe	H	Me	188-189
10	H	H	H	OMe	Me	180-181
11	H	H	Cl	F	Me	188-189
12	H	H	Cl	Me	Me	197-199
13	H	H	Cl	OMe	Me	204-205
14	H	H	F	OMe	Me	191-192
15	COOMe	H	H	H	Me	112-113
16	COOH	H	H	H	Me	168-169
17	COOH	H	Cl	H	Me	190-192
18	COOH	H	Cl	Me	Me	203-205
19	COOH	H	Cl	OMe	Me	231-232
20	COOH	H	F	OMe	Me	215-216
21	F	H	H	H	Me	120-122
22	Cl	H	H	H	Me	140-142
23	Br	H	H	H	Me	172-173
24	Me	H	H	H	Me	122-123
25	Ph	H	H	H	Me	165-167
26	COMe	H	H	H	Me	138-139
27	H	H	H	H	NH_2	188-189
28	H	H	F	H	NH_2	166-167
29	H	H	Cl	H	NH_2	168-169
30	H	H	Me	H	NH_2	181-182
31	H	H	MeO	H	NH_2	172-173
32	H	H	Cl	F	NH_2	118-119
33	H	H	Cl	Me	NH_2	117-119
34	H	H	Cl	OMe	NH_2	222-223
35	H	H	F	OMe	NH_2	102-103
36	COOH	H	Cl	OMe	NH_2	231-232
37	CH_2COOH	H	H	H	Me	130-132
38	H	H	OMe	OMe	Me	183-184
39	H	H	OMe	OMe	NH_2	222-223

CLAIMS

1. A compound which is a 2-phenylazulene of formula (I):



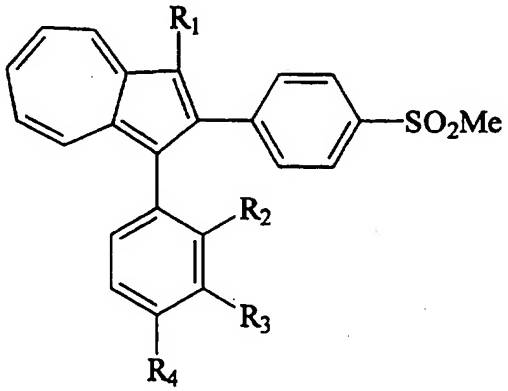
(I)

R_1 is hydrogen, lower alkoxycarbonyl, carboxy, carboxymethyl, a halogen, lower alkyl, phenyl or lower alkanoyl;

R_2, R_3 and R_4, which are the same or different, are hydrogen, lower alkyl, lower alkoxy or a halogen; and

X is lower alkyl or amino; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the 2-phenylazulene is of formula (II):



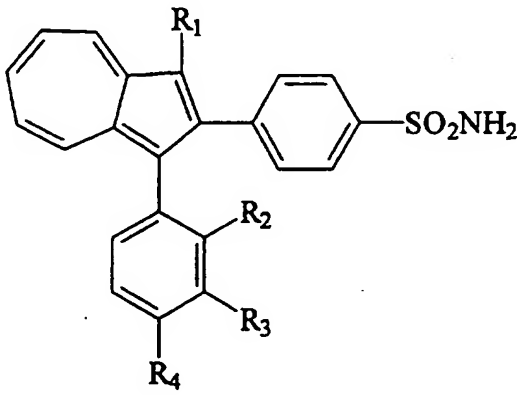
(II

wherein

R_1 is hydrogen, methoxycarbonyl, carboxy, fluorine, chlorine, bromine, methyl, phenyl or acetyl; and

R_2, R_3 and R_4, which are the same or different, are hydrogen, methyl, methoxy, fluorine or chlorine.

3. A compound according to claim 1 wherein the 2-phenylazulene is of formula (III):



(III)

wherein

R_1 is hydrogen, methoxycarbonyl, carboxy, fluorine, chlorine, bromine, methyl, phenyl or acetyl; and

R_2, R_3 and R_4, which are the same or different, are hydrogen, methyl, methoxy, fluorine or chlorine.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as an active ingredient, a compound as defined in any one of claims 1 to 3.

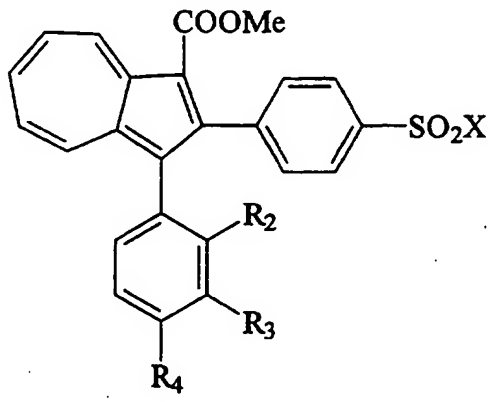
5. A compound as defined in any one of claims 1 to 3 for use in a method of treatment of the human or animal body by therapy or prophylaxis.

6. A compound as claimed in claim 5 for use as an inhibitor of cyclooxygenase-2.

7. A compound according to claim 6 for use in the treatment of inflammation, pain or fever.

8. Use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of inflammation, pain or fever.

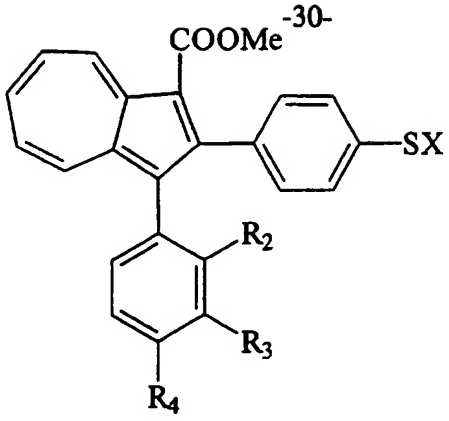
9. A process for producing a compound as defined in claim 1 wherein, in formula (I), R_1 is hydrogen and X is lower alkyl, which process comprises treating, with an acid, a compound of formula (X):



(X)

wherein X is lower alkyl and R_2, R_3 and R_4 are as defined in claim 1.

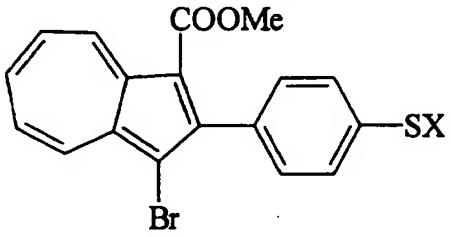
10. A process according to claim 9 which comprises the further step of producing the compound of formula (X) by oxidising a compound of formula (IX):



(IX)

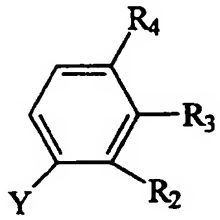
wherein X is lower alkyl and R_2, R_3 and R_4 are as defined in claim 1.

11. A process according to claim 10 which comprises the further step of producing the compound of formula (IX) by reacting a compound of formula (VII):



(VII)

wherein X is lower alkyl, with a compound of formula (VIII):

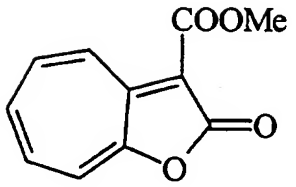


(VIII)

wherein Y is $B(OH)_2$ or $SnMe_3$ and R_2, R_3 and R_4 are as defined in claim 1.

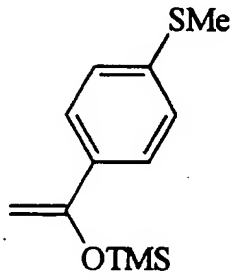
12. A process according to claim 11 which comprises the further step of producing the compound of formula (VII) by

(i) reacting a compound of formula (IV):



(IV)

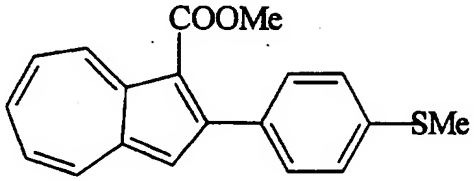
with a compound of formula (V):



(V)

wherein OTMS is a trimethylsilyloxy group; and

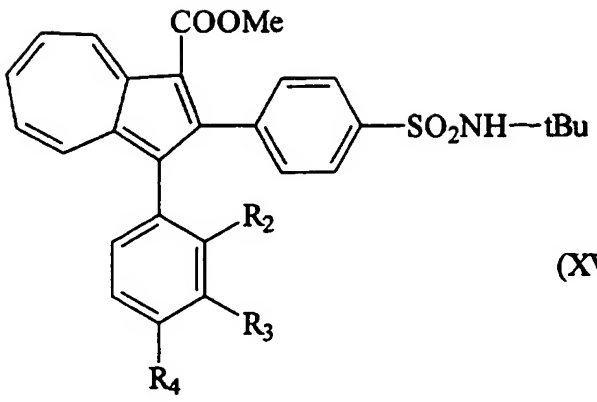
(ii) brominating the resulting compound of formula (VI):



(VI)

wherein X is as defined in claim 1, to yield the desired compound of formula (VII).

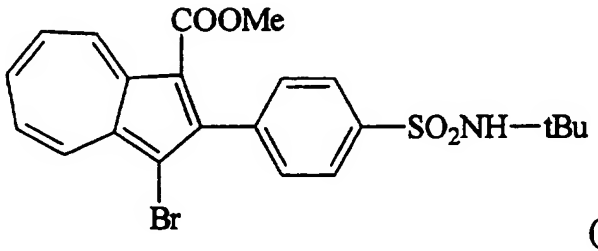
13. A process for producing a compound as defined in claim 1 wherein, in formula (I), R_1 is hydrogen and X is amino, which process comprises treating, with an acid, a compound of formula (XVI):



(XVI)

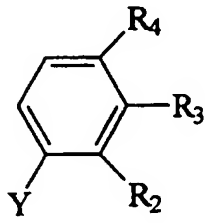
wherein R_2, R_3 and R_4 are as defined in claim 1.

14. A process according to claim 13 which comprises the further step of producing the compound of formula (XVI) by reacting a compound of formula (XV):



(XV)

with a compound of formula (VIII):

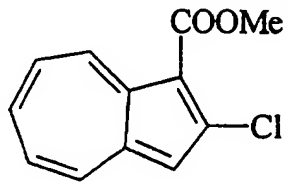


(VIII)

wherein Y is $B(OH)_2$ or $SnMe_3$ and R_2, R_3 and R_4 are as defined in claim 1.

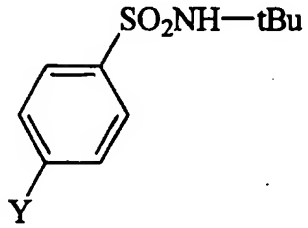
15. A process according to claim 14 which comprises the further step of producing the compound of formula (XV) by

(i) reacting a compound of formula (XII):



(XII)

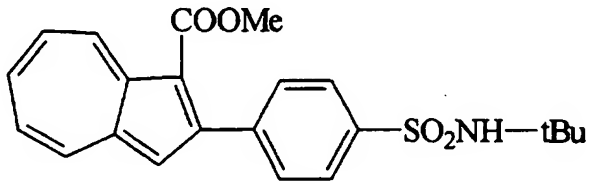
with a compound of formula XIII):



(XIII)

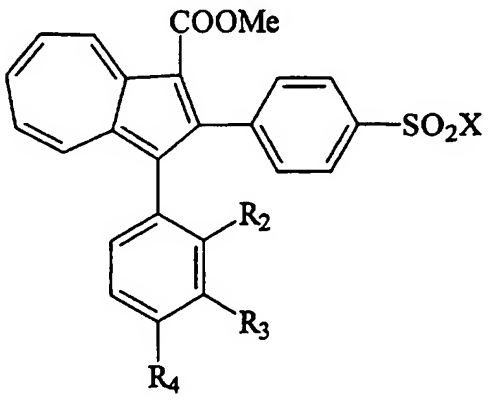
wherein Y is $B(OH)_2$ or $SnMe_3$; and

(ii) brominating the resulting compound of formula (XIV):



(XIV)

16. A process for producing a compound as defined in claim 1 wherein, in formula (I), R_1 is carboxy, which process comprises hydrolysing a compound of formula (XVIII):

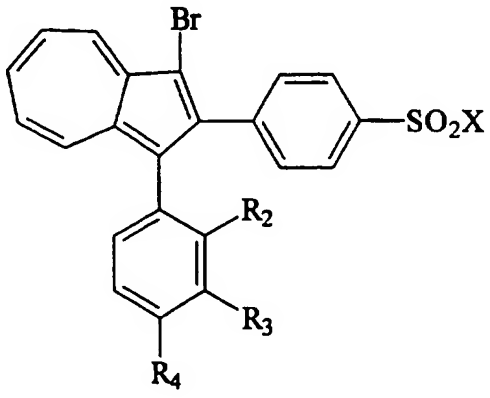


(XVIII)

wherein X, R_2, R_3 and R_4 are as defined in claim 1.

17. A process for producing a compound as defined in claim 1 wherein, in formula (I), R_1 is fluorine, chlorine or bromine, which process comprises halogenating a corresponding compound as defined in claim 1 wherein, in formula (I), R_1 is hydrogen.

18. A process for producing a compound as defined in claim 1 wherein, in formula (I), R_1 is lower alkyl or phenyl, which process comprises reacting a compound of formula (XXI):



(XXI)

wherein X, R_2, R_3 and R_4 are as defined in claim 1, with a compound of formula (XXII):

$$R_6—B(OH)_2 \qquad (XXII)$$

wherein R_6 is lower alkyl or phenyl.

19. A process for producing a compound as defined in claim 1 wherein, in formula (I),R_1 is lower alkanoyl, which process comprises acylating, by a Friedel-Crafts reaction, a corresponding compound as defined in claim 1 wherein, in formula (I), R_1 is hydrogen.

20. A process for producing a compound as defined in claim 1 wherein, in formula (I), R_1 is carboxymethyl, which process comprises:

(i) treating a corresponding compound as defined in claim 1 wherein, in formula (I), R_1 is lower alkanoyl, with sulphur in the presence of a secondary amine by the Wilgerodt-kindler reaction; and

(ii) hydrolysing the resulting thioamide derivative under acidic or basic conditions to yield the desired compound.

21. A process according to any one of claims 9 to 20 which comprises the further step of converting the resulting 2-phenylazulene of formula (I) into a pharmaceutically acceptable salt thereof.

22. A process as defined in any one of claims 9 to 21, substantially as hereinbefore described in any one of the Examples.

23. A compound produced by a process as defined in any one of claims 9 to 22.

24. A compound as defined in claim 1, specifically hereinbefore mentioned.

The Patent Office

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Application No:	GB 9725265.4	**Examiner:**	William Thomson
Claims searched:	1-24	**Date of search:**	4 February 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): C2C (CQN, CQT, CSF)

Int Cl (Ed.6): C07C 311/16, 317/14

Other: ONLINE:CAS-ONLINE, EDOC, WPI.

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
	NONE	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.